

Difference in Therapeutic Response Between Basal and Nonbasal Triple-Negative Breast Cancers

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The study described here, which nicely complements a study by Prat et al. that was recently published in *The Oncologist*, shows for the first time that triple-negative breast cancers are much more heterogeneous than basal breast cancers regarding the response to chemotherapy and the probability of response to molecularly targeted therapies.

Pratetal. report that triple-negative (TN) breast cancers (BCs) represent a more heterogeneous group than basal BCs [1]. TN BCs include basal and nonbasal tumors and show much more difference in patient age and gene expression profiles than basal BCs, which include TN and non-TN cases. These results confirm our previous observations [2] reported in a smaller series with several tumor features: age; pathological grade; mRNA expression of ESR1, PGR, and ERBB2 and markers of luminal (KRT18) and basal (KRT5 and KRT6A) epithelial lineage. Current efforts aim to define better systemic therapies for TN BCs [3, 4]. In this context, an important issue— even more relevant clinically than histological and molecular characterization—is whether this difference of homogeneity between TN BCs and basal BCs exists in terms of therapeutic response.

We tested this hypothesis in a large gene expression database of BCs including 33 public microarray data sets, representing 6,717 invasive BCs that were clinically annotated. A total of 645 samples were TN according to their immunohistochemistry status, and 584 were basal according to the PAM50 and claudin-low predictors [5, 6]. Within TN BCs, 315 were basal and 330 were nonbasal. Within basal BCs, 330 were TN and 255 were non-TN. Univariate analyses (Table 1) compared several histoclinical and molecular variables related to therapeutic response in the two TN subgroups (basal vs. nonbasal) and in the two basal subgroups (TN vs. non-TN).

The rate of pathological complete response (pCR) to neo-adjuvant anthracycline-based chemotherapy was 33% in the 324 informative TN cases and 38% in the 226 informative basal cases. More important, the pCR rate and all tested variables classically linked to chemosensitivity (pathological tumor size,

genomic grade index, *MKI67* mRNA expression) were very different between the two TN subgroups but were not different between the two basal subgroups. Among the TN BCs, higher pCR rate, smaller pT3 size, higher genomic grade index, and *MKI67* mRNA expression were found in basal samples compared with nonbasal samples.

We observed similar results with targets of molecularly targeted therapies under development for TN BCs. To exploit the DNA repair defect observed within basal BCs, poly (ADP-ribose) polymerase or "PARP" inhibitors have been evaluated in TN BCs. Initial promising results with olaparib [7] did not hold in the following phase III trial that enrolled 519 TN patients [8]. One explanation was the absence of proper patient selection. Our present analysis reinforces this hypothesis: The genome instability, assessed by the Carter's gene expression signature, PARP1 mRNA expression, or gene expression signature of homologous recombination and ATR-BRCA pathway, was much more heterogeneous in TN BCs than in basal BCs. Similarly, the activation status of 18 biological pathways [9] including potential therapeutic targets of TN BCs (i.e., EGFR, PIK3CA [also known as PI3K], or SRC) or therapeutic response-associated markers (i.e., TP53 [also known as P53], TP63 [also known as P63], or KRAS) was much more homogeneous in basal BCs.

We show that TN BCs are much more heterogeneous than basal BCs regarding the response to chemotherapy and the probability of response to targeted therapies. This result, together with the study by Prat et al. [1], calls for caution in the interpretation and design of clinical trials dedicated to otherwise nonspecified TN BCs and warrants the search for molecular markers of basal BCs that are more clinically applicable than gene expression profiling.

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DISCLOSURES

The authors indicated no financial relationships.

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Table 1. Comparison of breast cancer subgroups within the triple-negative group and the basal group

Variable n Non-basil subgroup (r. = 330) p³ n Non-Th Subgroup (r. = 350) p Pathological complete response 324 3.226-30 26 3.226-30 26 3.226-30 26 3.226-30 26 3.226-30 26 3.226-30 26 3.226-30 26 3.226-30 26 4.568-30 345 (68%) 345 (68%) 34 (68%) 34 (68%) 34 (68%) 34 (68%) 34 (68%) 34 (68%) 34 (68%) 36 (68%) 35 (38,28%) 29 (22%) 66 40 (29%) 42 (68%) 39 (25%) 40 (29%) 29 (23%) 40 (29%) 29 (23%) 40 (29%) 29 (23%) 40 (29%) 29 (23%) 40 (29%) 29 (23%) 40 (29%) 29 (23%) 40 (29%) 29 (23%) 40 (29%) 29 (23%) 40 (29%) 29 (23%) 40 (29%) 29 (23%) 40 (29%) 29 (23%) 40 (29%) 29 (23%) 40 (29%) 29 (23%) 40 (29%) 29 (23%) 40 (29%) 29 (23%) 40 (29%) 29 (23%) 40 (29%) 29 (23%) 40 (29%) 29 (23%)	Variable	TN breast cancers (n = 645)				Basal breast cancers (n = 585)			
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Yes 108 42 (26%) 66 (41%) 87 21 (32%) 66 (41%) Pathological tumor size 267 3.51E-02 272 <td>Pathological complete response</td> <td>324</td> <td></td> <td></td> <td>3.22E-03</td> <td>226</td> <td></td> <td></td> <td>.229</td>	Pathological complete response	324			3.22E-03	226			.229
Pathological tumor size 267 3.51E-02 272 4029() 29 (22%) 40 (29%) 29 (22%) 40 (29%) 29 (22%) 40 (29%) 29 (22%) 40 (20%) 29 (22%) 40 (20%) 29 (22%) 40 (20%) 29 (22%) 40 (20%) 20 (15%) 40 (20%) 20 (15%) 40 (20%) 20 (15%) 40 (20%) 20 (15%) 40 (20%) 20 (15%) 40 (20%) 20 (15%) 40 (20%) 20 (15%) 40 (20%) 20 (15%) 40 (20%) 20 (15%) 40 (20%)	No	216	122 (74%)	94 (59%)		139	45 (68%)	94 (59%)	
PT1	Yes	108	42 (26%)	66 (41%)		87	21 (32%)	66 (41%)	
TTZ 148 64 (48%) 84 (63%) 163 79 (57%) 84 (63%) 179 TM 84 (63	Pathological tumor size	267			3.51E-02	272			.406
σT3 52 32 (24%) 20 (15%) 40 20 (14%) 20 (15%) Genomic grade index 608 195 (65%) 284 (92%) 478 194 (92%) 284 (92%) High 479 195 (65%) 284 (92%) 478 194 (92%) 284 (92%) MKI67 mRNA expression³ 644 3.07 3.87 3.60€-15 584 3.56 3.87 7 PARPI mRNA expression³ 645 0.36 0.72 1.34€-14 585 0.72 0.72 .3 Homologous recombination (KEGG pathway)² 645 0.13 0.38 1.91E-24 585 0.32 0.38 3 ATR-BRCA pathway (Biocarta)² 645 0.13 0.38 1.91E-24 585 0.32 0.38 3 ATR-BRCA pathway (Biocarta)² 645 0.13 0.48 4.08E-18 585 0.42 0.72 .3 Stable 187 141 (45%) 46 (14%) 89 43 (17%) 46 (14%) 46 (14%) 46 (14%) 46 (14%)	pT1	67	38 (28%)	29 (22%)		69	40 (29%)	29 (22%)	
Genomic grade index 608 8.86E-16 520 284 (92%) 284 (92%) Ligh 479 195 (65%) 284 (92%) 478 194 (92%) 284 (92%) Low 129 103 (35%) 26 (8%) 42 16 (8%) 26 (8%) MK167 mRNA expression ¹⁶ 644 3.07 3.87 3.60E-15 584 3.56 3.87 7.7 PARP1 mRNA expression ¹⁶ 645 0.36 0.72 1.34E-14 585 0.72 0.72 .3 Homologous recombination (KEGG pathway) ¹⁶ 645 0.13 0.38 1.91E-24 585 0.32 0.38 3 ATR-BRCA pathway (Biocarta) ¹⁶ 645 0.23 0.48 4.80E-18 585 0.43 0.48 .0 Carter's gene expression signature 645 0.23 0.48 4.80E-18 585 0.43 0.48 .0 Instable 187 141 (45%) 46 (14%) 496 212 (83%) 284 (86%) Lostale 198 0.74 (5	pT2	148	64 (48%)	84 (63%)		163	79 (57%)	84 (63%)	
High 479 195 (65%) 284 (92%) 478 194 (92%) 284 (92%) 478 194 (92%) 284 (92%) 103 (35%) 26 (8%) 42 16 (8%) 26 (pT3	52	32 (24%)	20 (15%)		40	20 (14%)	20 (15%)	
Low 129 103 (35%) 26 (8%) 42 16 (8%) 26 (8%) MKI67 mRNA expression ^b 644 3.07 3.87 3.60E-15 584 3.56 3.87 7 PARPI mRNA expression ^b 645 0.36 0.72 1.34E-14 585 0.72 0.72 3.8 Homologous recombination (KEGG pathway) ^C 645 0.13 0.38 1.91E-24 585 0.32 0.38 3 ATR-BRCA pathway (Biocarta) ^C 645 0.23 0.48 4.80E-18 585 0.43 0.48 0.38 Stable 187 141 (45%) 46 (14%) 89 43 (17%) 46 (14%) 46 (14%) 496 212 (83%) 284 (86%) 40 (14%) <t< td=""><td>Genomic grade index</td><td>608</td><td></td><td></td><td>8.86E-16</td><td>520</td><td></td><td></td><td>.870</td></t<>	Genomic grade index	608			8.86E-16	520			.870
MKI67 mRNA expression b 644 3.07 3.87 3.60E-15 584 3.56 3.87 7 PARPI mRNA expression b 645 0.36 0.72 1.34E-14 585 0.72 0.72 .8 Homologous recombination (KEGG pathway) ^c 645 0.13 0.38 1.91E-24 585 0.32 0.38 3 ATR-BRCA pathway (Biocarta) ^c 645 0.23 0.48 4.80E-18 585 0.43 0.48 0.48 Carter's gene expression signature 645 0.23 46 (14%) 46 (14%) 489 43 (17%) 46 (14%) 458 174 (55%) 284 (86%) 496 212 (83%) 284 (86%) 4.07E-02 585 0.51 0.56 8 BCAT ^d 645 0.53 0.56 4.07E-02 585 0.51 0.56 8 BCAT ^d 645 0.53 0.56 4.07E-02 585 0.51 0.56 8 BCAT ^d 645 0.51 0.65 1.46E-07	High	479	195 (65%)	284 (92%)		478	194 (92%)	284 (92%)	
PARPI mRNA expression ^b 645 0.36 0.72 1.34E-14 585 0.72 0.72 8.8 Homologous recombination (KEGG pathway) ^c 645 0.13 0.38 1.91E-24 585 0.32 0.38 3 ATR-BRCA pathway (Biocarta) ^c 645 0.23 0.48 4.80E-18 585 0.43 0.48 4.8 Carter's gene expression signature 645 0.23 0.48 4.80E-18 585 0.43 0.48 4.8 Stable 187 141 (45%) 46 (14%) 496 212 (83%) 284 (66%) 496 212 (83%) 284 (66%) 496 212 (83%) 284 (66%) 496 212 (83%) 284 (86%) 407E-02 585 0.51 0.55 8 8 665 0.51 0.65 4.07E-02 585 0.51 0.55 8 8 65 0.51 0.65 1.46E-07 585 0.62 0.65 3 6 62 0.65 3 4 6.62 0.62 0.	Low	129	103 (35%)	26 (8%)		42	16 (8%)	26 (8%)	
Homologous recombination (KEGG pathway)° 645 0.13 0.38 1.91E-24 585 0.32 0.38 3 ATR-BRCA pathway (Biocarta)° 645 0.23 0.48 4.80E-18 585 0.43 0.48 0.48 Stable 187 141 (45%) 46 (14%) 89 43 (17%) 46 (14%) 46 (14%) 496 212 (83%) 284 (86%) 496 212 (83%) 284 (86%) 496 212 (83%) 284 (86%) 496 212 (83%) 284 (86%) 496 212 (83%) 284 (86%) 496 212 (83%) 284 (86%) 496 212 (83%) 284 (86%) 496 212 (83%) 284 (86%) 496 212 (83%) 284 (86%) 496 212 (83%) 284 (86%) 496 212 (83%) 284 (86%) 496 212 (83%) 284 (86%) 496 212 (83%) 284 (86%) 496 212 (83%) 284 (86%) 496 212 (83%) 284 (86%) 496 212 (83%) 284 (86%) 496 212 (83%) 284 (86%) 496 212 (83%) 484 (81%	MKI67 mRNA expression ^b	644	3.07	3.87	3.60E-15	584	3.56	3.87	7.18E-03
ATR-BRCA pathway (Biocarta)² 645 0.23 0.48 4.80E-18 585 0.43 0.48 0.68 Carter's gene expression signature 645	PARP1 mRNA expression ^b	645	0.36	0.72	1.34E-14	585	0.72	0.72	.840
Carter's gene expression signature 645 2.49E-18 585	Homologous recombination (KEGG pathway) ^c	645	0.13	0.38	1.91E-24	585	0.32	0.38	3.21E-02
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Unstable 458 174 (55%) 284 (86%) 496 212 (83%) 284 (86%) AKTd 645 0.53 0.56 4.07E-02 585 0.51 0.56 8 BCATd 645 0.48 0.84 4.26E-24 585 0.8 0.84 0.6 E2F1d 645 0.51 0.65 1.46E-07 585 0.62 0.65 3 EGFRd 645 0.55 0.37 2.66E-12 585 0.42 0.37 0.6 ERd 645 0.07 0.02 7.03E-17 585 0.04 0.02 1 HER2d 645 0.47 0.42 1.18E-03 585 0.49 0.42 2 IFNxd 645 0.6 0.63 1.47 585 0.73 0.63 3 IFNyd 645 0.45 0.7 0.75 330 585 0.81 0.75 3 IFNyd 645 0.45 0.21	Carter's gene expression signature	645			2.49E-18	585			.354
AKT ^d 645 0.53 0.56 4.07E-02 585 0.51 0.56 8 BCAT ^d 645 0.48 0.84 4.26E-24 585 0.8 0.84 0.84 E2FI ^d 645 0.51 0.65 1.46E-07 585 0.62 0.65 3.3 EGFR ^d 645 0.55 0.37 2.66E-12 585 0.42 0.37 0.02 ER ^d 645 0.07 0.02 7.03E-17 585 0.04 0.02 1 HER2 ^d 645 0.47 0.42 1.18E-03 585 0.49 0.42 2 IFNα ^d 645 0.6 0.63 1.147 585 0.73 0.63 3.3 IFNγ ^d 645 0.45 0.7 0.75 3.30 585 0.81 0.75 3.3 IFNγ ^d 645 0.45 0.70 0.75 3.30 585 0.62 0.66 0.73 1 TP53 ^d 645 0.45 0.73 9.43E-34 585 0.66 0.73 1 TP53 ^d 645 0.47 0.62 1.10E-12 585 0.59 0.62 PR ^d 645 0.49 0.4 9.65E-04 585 0.07 0.05 9 SRC ^d 645 0.49 0.4 9.65E-04 585 0.4 0.4 0.4 3.8 STAT3 ^d 645 0.56 0.48 8.57E-09 585 0.5 0.44 0.36 44 TP63 ^d 645 0.52 0.54 0.63 7.96E-07 585 0.57 0.63 22 KKAS ^d 645 0.52 0.67 2.10E-19 585 0.57 0.63 22 KKAS ^d 645 0.52 0.67 2.10E-19 585 0.57 0.63	Stable	187	141 (45%)	46 (14%)		89	43 (17%)	46 (14%)	
BCAT ^d 645 0.48 0.84 4.26E-24 585 0.8 0.84 0.84 E2F1 ^d 645 0.51 0.65 1.46E-07 585 0.62 0.65 3.3 EGFR ^d 645 0.55 0.37 2.66E-12 585 0.42 0.37 0.6 Egt ^d 645 0.07 0.02 7.03E-17 585 0.42 0.37 0.6 HER2 ^d 645 0.47 0.42 1.18E-03 585 0.49 0.42 2 IFNα ^d 645 0.6 0.63 1.147 585 0.73 0.63 3.3 IFNγ ^d 645 0.7 0.75 330 585 0.81 0.75 3.3 MYC ^d 645 0.45 0.73 9.43E-34 585 0.66 0.73 1 TP53 ^d 645 0.45 0.21 0.1 1.86E-26 585 0.12 0.1 2 PR ^d 645 0.47 0.62 1.10E-12 585 0.59 0.62 3.3 <	Unstable	458	174 (55%)	284 (86%)		496	212 (83%)	284 (86%)	
E2F1 ^d 645 0.51 0.65 1.46E-07 585 0.62 0.65 3.5 EGFR ^d 645 0.55 0.37 2.66E-12 585 0.42 0.37 3.6 ER ^d 645 0.07 0.02 7.03E-17 585 0.04 0.02 1 ER ^d 645 0.47 0.42 1.18E-03 585 0.49 0.42 2 IFNα ^d 645 0.6 0.63 1.47 585 0.73 0.63 3.5 IFNγ ^d 645 0.7 0.75 3.30 585 0.81 0.75 3.5 IFNγ ^d 645 0.45 0.45 0.73 9.43E-34 585 0.66 0.73 1 TP53 ^d 645 0.21 0.1 1.86E-26 585 0.12 0.1 2 PIK3CA ^d 645 0.47 0.62 1.10E-12 585 0.59 0.62 EFR ^d 645 0.49 0.49 0.4 9.65E-04 585 0.4 0.4 0.4 3.5 EFR ^d 645 0.56 0.48 8.57E-09 585 0.5 0.4 0.4 3.6 EFR ^d 645 0.52 0.36 2.30E-07 585 0.4 0.4 0.36 4 EFR ^d 645 0.52 0.67 2.10E-19 585 0.57 0.63 2 EFR ^d 645 0.52 0.67 2.10E-19 585 0.57 0.63 2	AKT ^d	645	0.53	0.56	4.07E-02	585	0.51	0.56	8.78E-03
EGFR ^d 645 0.55 0.37 2.66E-12 585 0.42 0.37 0.02 $^{\circ}$ C.6E-12 585 0.42 0.37 0.02 $^{\circ}$ C.6E-12 585 0.42 0.37 0.02 1 $^{\circ}$ C.6E-12 585 0.04 0.02 1 $^{\circ}$ C.6E-12 585 0.04 0.02 1 $^{\circ}$ C.6E-12 585 0.04 0.02 1 $^{\circ}$ C.6E-12 585 0.49 0.42 2 $^{\circ}$ C.6E-12 585 0.49 0.42 2 $^{\circ}$ C.6E-12 585 0.49 0.42 2 $^{\circ}$ C.6E-12 585 0.73 0.63 3.30 $^{\circ}$ C.6E-12 585 0.73 0.63 3.30 $^{\circ}$ C.6E-12 585 0.73 0.63 3.30 $^{\circ}$ C.6E-12 585 0.81 0.75 3.30 $^{\circ}$ C.6E-12 585 0.66 0.73 1 $^{\circ}$ C.7E-12 585 0.66 0.73 1 $^{\circ}$ C.7E-12 585 0.62 0.73 0.62 1.7E-12 585 0.59 0.62 1.7E-12 585 0.7E-12 0.1 0.1 0.1 0.1 0.1E-12 585 0.7E-12 0.1 0.1 0.1 0.1 0.1 0.1 0.1 0.1 0.1 0.1	BCAT ^d	645	0.48	0.84	4.26E-24	585	0.8	0.84	.060
ER ^d 645 0.07 0.02 7.03E-17 585 0.04 0.02 1 HER2 ^d 645 0.47 0.42 1.18E-03 585 0.49 0.42 2 IFNα ^d 645 0.6 0.63 .147 585 0.73 0.63 .3 MYC ^d 645 0.7 0.75 .330 585 0.81 0.75 .3 MYC ^d 645 0.45 0.73 9.43E-34 585 0.66 0.73 1 TP53 ^d 645 0.21 0.1 1.86E-26 585 0.12 0.1 2 PR ^d 645 0.47 0.62 1.10E-12 585 0.59 0.62 .3 SRC ^d 645 0.06 0.05 8.44E-07 585 0.07 0.05 9 SRC ^d 645 0.49 0.4 9.65E-04 585 0.4 0.4 8 STAT3 ^d 645 0.56 0.48 8.57E-09 585 0.5 0.48 .3 TP63 ^d <td< td=""><td>E2F1^d</td><td>645</td><td>0.51</td><td>0.65</td><td>1.46E-07</td><td>585</td><td>0.62</td><td>0.65</td><td>.391</td></td<>	E2F1 ^d	645	0.51	0.65	1.46E-07	585	0.62	0.65	.391
HER2 ^d 645 0.47 0.42 1.18E-03 585 0.49 0.42 2.1FNα ^d 645 0.6 0.63 1.147 585 0.73 0.63 3.31 1FNγ ^d 645 0.7 0.75 3.30 585 0.81 0.75 3.3 MYC ^d 645 0.45 0.73 9.43E-34 585 0.66 0.73 1 TP53 ^d 645 0.21 0.1 1.86E-26 585 0.12 0.1 2. PIK3CA ^d 645 0.47 0.62 1.10E-12 585 0.59 0.62 3.3 PR ^d 645 0.06 0.05 8.44E-07 585 0.07 0.05 9 SRC ^d 645 0.49 0.4 9.65E-04 585 0.4 0.4 0.4 8.5TAT3 ^d 645 0.56 0.49 0.48 8.57E-09 585 0.5 0.4 0.4 0.4 8.5TAT3 ^d 645 0.52 0.36 2.30E-07 585 0.57 0.63 2.5 KRAS ^d 645 0.52 0.67 0.63 7.96E-07 585 0.57 0.63 2.5 KRAS ^d 645 0.52 0.67 0.67 2.10E-19 585 0.62 0.67 8.5 C.67 0.67 0.67 0.67 0.67 8.5 C.67 0.67 0.67 8.5 C.67 0.67 0.67 0.67 0.67 0.67 0.67 0.67 0	EGFR ^d	645	0.55	0.37	2.66E-12	585	0.42	0.37	.094
IFNα ^d 645 0.6 0.63 1.47 585 0.73 0.63 3.5 IFNγ ^d 645 0.7 0.75 3.30 585 0.81 0.75 3.5 MYC ^d 645 0.45 0.73 9.43E-34 585 0.66 0.73 1 TPS3 ^d 645 0.21 0.1 1.86E-26 585 0.12 0.1 2 PIK3CA ^d 645 0.47 0.62 1.10E-12 585 0.59 0.62 3.5 PR ^d 645 0.06 0.05 8.44E-07 585 0.07 0.05 9 SRC ^d 645 0.49 0.4 9.65E-04 585 0.4 0.4 0.4 3.5 STAT3 ^d 645 0.56 0.56 0.48 8.57E-09 585 0.5 0.4 0.4 0.36 4 TPG3 ^d 645 0.52 0.63 7.96E-07 585 0.57 0.63 2 KRAS ^d 645 0.52 0.67 0.63 7.96E-07 585 0.62 0.67 8.5 KRAS ^d 645 0.52 0.67 0.63 7.96E-07 585 0.62 0.67 8.5 KRAS ^d 645 0.52 0.67 0.67 2.10E-19 585 0.62 0.67 8.5 CRAS ^d 645 0.52 0.67 0.67 2.10E-19 585 0.62 0.67 8.5 CRAS ^d 645 0.52 0.67 0.67 8.5 CRAS ^d 645 0.52 0.67 0.67 0.67 0.67 0.67 0.67 0.67 0.67	ER ^d	645	0.07	0.02	7.03E-17	585	0.04	0.02	1.03E-08
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	HER2 ^d	645	0.47	0.42	1.18E-03	585	0.49	0.42	2.17E-03
MYC^d 645 0.45 0.73 9.43E-34 585 0.66 0.73 1 $TP53^d$ 645 0.21 0.1 1.86E-26 585 0.12 0.1 2 $PIK3CA^d$ 645 0.47 0.62 1.10E-12 585 0.59 0.62 3.1 PR^d 645 0.06 0.05 8.44E-07 585 0.07 0.05 9 SRC^d 645 0.49 0.4 9.65E-04 585 0.4 0.4 0.4 3.5 $STAT3^d$ 645 0.56 0.48 8.57E-09 585 0.5 0.48 3.2 $TGFβ^d$ 645 0.52 0.36 2.30E-07 585 0.40 0.36 4 $TP63^d$ 645 0.52 0.63 7.96E-07 585 0.57 0.63 2 SRC^d 645 0.52 0.67 2.10E-19 585 0.62 0.67 8	$IFN\alpha^d$	645	0.6	0.63	.147	585	0.73	0.63	.395
TP53 ^d 645 0.21 0.1 1.86E-26 585 0.12 0.1 2 PIK3CA ^d 645 0.47 0.62 1.10E-12 585 0.59 0.62 PR ^d 645 0.06 0.05 8.44E-07 585 0.07 0.05 9 SRC ^d 645 0.49 0.4 9.65E-04 585 0.4 0.4 0.4 8. STAT3 ^d 645 0.56 0.48 8.57E-09 585 0.5 0.48 TGFβ ^d 645 0.52 0.36 2.30E-07 585 0.47 0.36 4 TP63 ^d 645 0.52 0.63 7.96E-07 585 0.57 0.63 2.2 KRAS ^d 645 0.52 0.67 2.10E-19 585 0.62 0.67 8	$IFN\gamma^d$	645	0.7	0.75	.330	585	0.81	0.75	.355
PIK3CA ^d 645 0.47 0.62 $1.10E-12$ 585 0.59 0.62 0.52 0.59 0.62 0.59 0.59 0.62 0.59 0.59 0.62 0.59 <	MYC ^d	645	0.45	0.73	9.43E-34	585	0.66	0.73	1.95E-03
PR^d 645 0.06 0.05 8.44E-07 585 0.07 0.05 9 9 SRC ^d 645 0.49 0.4 9.65E-04 585 0.4 0.4 8.5TAT3 ^d 645 0.56 0.48 8.57E-09 585 0.5 0.48 2.2 TGFβ ^d 645 0.52 0.36 2.30E-07 585 0.44 0.36 4 TP63 ^d 645 0.54 0.63 7.96E-07 585 0.57 0.63 2.2 KRAS ^d 645 0.52 0.67 2.10E-19 585 0.62 0.67 8	TP53 ^d	645	0.21	0.1	1.86E-26	585	0.12	0.1	2.37E-05
SRC^d 645 0.49 0.4 9.65E-04 585 0.4 0.4 0.4 8.5 $STAT3^d$ 645 0.56 0.48 8.57E-09 585 0.5 0.48 2.2 $STAT3^d$ 645 0.52 0.36 2.30E-07 585 0.44 0.36 4 $STAT3^d$ 645 0.54 0.63 7.96E-07 585 0.57 0.63 2 $STAT3^d$ 645 0.52 0.67 2.10E-19 585 0.62 0.67 8.5 $STAT3^d$	PIK3CA ^d	645	0.47	0.62	1.10E-12	585	0.59	0.62	.184
$STAT3^d$ 645 0.56 0.48 8.57E-09 585 0.5 0.48 2.3 $TGF\beta^d$ 645 0.52 0.36 2.30E-07 585 0.44 0.36 4 $TP63^d$ 645 0.54 0.63 7.96E-07 585 0.57 0.63 2 $RRAS^d$ 645 0.52 0.67 2.10E-19 585 0.62 0.67 8	PR^d	645	0.06	0.05	8.44E-07	585	0.07	0.05	9.74E-11
TGF $β$ ^d 645 0.52 0.36 2.30E-07 585 0.44 0.36 4 TPG3 ^d 645 0.54 0.63 7.96E-07 585 0.57 0.63 2 KRAS ^d 645 0.52 0.67 2.10E-19 585 0.62 0.67 8	SRC ^d	645	0.49	0.4	9.65E-04	585	0.4	0.4	.864
TPG3 ^d 645 0.54 0.63 7.96E-07 585 0.57 0.63 2 KRAS ^d 645 0.52 0.67 2.10E-19 585 0.62 0.67 8	STAT3 ^d	645	0.56	0.48	8.57E-09	585	0.5	0.48	.282
KRAS ^d 645 0.52 0.67 2.10E-19 585 0.62 0.67 8	TGF $eta^{ extsf{d}}$	645	0.52	0.36	2.30E-07	585	0.44	0.36	4.17E-02
	TP63 ^d	645	0.54	0.63	7.96E-07	585	0.57	0.63	2.58E-03
TUE 0	KRAS ^d	645	0.52	0.67	2.10E-19	585	0.62	0.67	8.64E-03
INF $lpha^{\omega}$ 645 0.67 0.72 0.092 585 0.68 0.72 0	$TNF \alpha^d$	645	0.67	0.72	0.092	585	0.68	0.72	0.428

^aFisher's exact test for qualitative variables with discrete categories, and Wilcoxon test for continuous variables. *p* values under 5% are displayed with the E notation, where E represents times 10 raised to the power of the following exponent.

Abbreviation: TN, triple negative.

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EDITOR'S NOTE: Drs. Pratetal. have reviewed this letter and agree with the reported findings but have chosen not to respond formally.

^bMean mRNA expression of Affymetrix (Santa Clara, CA, http://www.affymetrix.com) probeset ID: 205225_at for MKI67, 208305_at for PARP1.

 $^{^{\}mathrm{c}}$ Mean metagene score.

 $^{^{\}rm d} Mean \, activation \, score.$